Maintenance therapy for cryptococcosis in patients with AIDS after successful primary therapy: oral fluconazole (300 mg daily) versus oral itraconazole (300 mg daily)

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INTRODUCTION

In patients with AIDS, cryptococcosis is the most common life-threatening fungal infection, having been described in 5-10% and in 15-30% of patients in western countries and in sub-Saharan Africa, respectively [1,2]. A high relapse rate (50–60%) has been widely documented after discontinuation of primary therapy [3,4]. Lifelong suppressive treatment is therefore currently recommended for patients who have successfully completed the initial therapy. Fluconazole and itraconazole have so far been considered the drugs of choice, owing to their oral administration and lack of serious toxic effects [5–9].

For the main purpose of comparing the efficacy and tolerability of these drugs, we initiated in 1991 a prospective randomized study on maintenance therapy for cryptococcosis in AIDS patients with oral 300 mg/daily of either fluconazole or itraconazole. The study was interrupted in December 1996 after the introduction of the new, potent antiretroviral drugs that have significantly affected the natural history of HIV-related infections.

PATIENTS AND METHODS

From June 1991, all consecutive AIDS patients who had successfully completed primary therapy, as previously defined [10], for culture-proven acute cryptococcal meningitis or extrameningeal disseminated cryptococcosis were openly randomized in 1:1 proportion to receive either fluconazole or itraconazole as lifelong maintenance treatment. Informed consent was obtained from all patients. Both drugs were given as capsules at the dosage of 300 mg once a day. Patients with a history of intolerance to azoles were excluded.

Cerebrospinal fluid (CSF) cultures, serum and CSF cryptococcal latex agglutination antigen (CLLA) test (Latex-Crypto Antigen Detection System, Immuno-Mycologics, Norman, OK, USA), blood cultures and urine cultures were performed: at enrollment, at months 2, 4, and 6, and every 3 months thereafter (or earlier whenever a relapse was clinically suspected).

The major endpoints were death and cryptococcosis relapse; additionally, adverse events requiring drug withdrawal were recorded. Drop-out was defined as discontinuation of therapy for more than 2 weeks, and relapse as the re-emergence of clinical cryptococcosis with positive blood or CSF culture(s).

In case of treatment withdrawal due to adverse events evoked by one of the two drugs under evaluation, maintenance therapy was pursued with the other drug.

Statistical analysis

Baseline characteristics, relapse rates and side effects of the treatment groups were compared and analyzed with the chi-squared test, Fisher exact test and Mantel–Haenzel test, to examine differences in proportions. The probability of survival, based on intention-to-treat analysis according to the initial treatment assignment, was estimated until death or cryptococcosis relapse according to the Kaplan–Meier method, and the treatment groups were compared by the log-rank test.

RESULTS

The 40 patients (35 males, 5 females; mean age 34.9 years; 36 intravenous drug users, three homosexuals

and one heterosexual) eligible for the study had a mean $CD4^+$cell count of 50.2/mm^3 (range 4–311); mean CLLA was 286.9 in CSF (range 0–4096) and 2249.3 in serum (range 8–8192). Nineteen were assigned to receive fluconazole, and 21 itraconazole. The two groups were comparable with respect to both baseline characteristics and total dose of amphotericin B administered over the duration of primary treatment (mean 693 mg (range 463–993 mg) and 618 mg (range 436–1316 mg) for the fluconazole and itraconazole groups, respectively). Supplemental flucytosine (mean daily dosage 112.7 mg/kg per day for a mean of 10 days) had been administered to 13 fluconazole and to 18 itraconazole patients; flucytosine was not administered in nine cases because of low white blood cell (WBC) (<1000/mm^3) and/or platelet (<50 000/mm^3) counts. At enrollment, all patients were symptom-free.

The median follow-up duration was 394.6 days (range 69–1264).

Antiretroviral treatment was ongoing for eight patients in the fluconazole group and seven in the itraconazole group (zidovudine monotherapy in 14 patients and zidovudine plus didanosine in one patient); the length of antiretroviral treatment in the two groups was not statistically different.

Two drop-outs were recorded, one in each arm, having spontaneously interrupted therapy at days 59 and 321, respectively, for longer than 2 weeks. Both patients developed a culture-proven cryptococcal relapse.

Failure of maintenance therapy was documented in only one itraconazole patient, who relapsed after 101 days of treatment, and died while on retreatment with amphotericin B.

Severe adverse reactions were observed only in patients under itraconazole treatment (19%; P=0.06, Fisher exact test): gastrointestinal symptoms in two patients (at days 34 and 193), skin rash in one patient (at day 92), and acute pancreatitis (at day 614) in one more patient (who did not receive didanosine). These four patients were shifted to fluconazole, without any further side effects. Itraconazole had to be discontinued in four additional cases (19%) due to the occurrence of esophageal candidiasis, defined as severe thrush and dysphagia, which resolved after intravenous amphotericin B treatment.

In summary, therapy discontinuation was required for 8 of 21 (38.1%) patients originally assigned to the itraconazole arm, while no patients on fluconazole treatment required withdrawal (P=0.002, Fisher exact test).

The causes of death among patients assigned to itraconazole treatment were wasting syndrome and AIDS dementia complex in 12 cases, disseminated *Mycobacterium avium* complex infection in two patients, disseminated cytomegalovirus infection in two patients, cerebral toxoplasmosis in one case, Kaposi's sarcoma in one case, and cryptococcal relapse in one case. At the time of the analysis, two patients of the itraconazole arm, but further shifted to fluconazole, were still alive.

Of the patients treated with fluconazole, two were still alive, one was lost at follow-up at 300 days while still in good condition, and eight had died from wasting syndrome, two from cerebral toxoplasmosis, one from pneumonia, two from *Mycobacterium avium* complex infection, one from *Staphylococcus aureus* endocarditis, and one from disseminated cytomegalovirus infection. Except for the patient with cryptococcosis relapse, cryptococcosis was ruled out as the cause of death on the basis of negative mycologic assessment by blood culture (all cases) and CSF culture (performed in 15 cases with central nervous system symptoms).

Survival estimates performed on an intention-to-treat basis did not reveal significant differences between the two study drugs (Figure 1).

DISCUSSION

When this study was started, there was no definite agreement on drug of choice, dosage and duration of maintenance therapy for cryptococcosis in AIDS patients.

Because of their proven efficacy in cryptococcosis, we decided to compare itraconazole and fluconazole by efficacy and tolerability in long-term treatment and oral administration; a 300-mg daily dosage was chosen on empirical basis.

The efficacy and safety of the two drugs in therapy for cryptococcosis in AIDS patients have already been compared in two studies, only recently reporting different dosages and follow-up duration.

Saag et al [7] compared oral fluconazole and itraconazole at a dosage of 200 mg/daily, in 107 patients during a 52-week follow-up period. The study revealed a significantly greater relapse rate in itraconazole- than in fluconazole-treated patients (24% versus 4%, respectively). Toxicity requiring drug discontinuation was observed in seven (6.5%) patients.

The efficacy and safety of fluconazole in comparison to itraconazole as an 8-week consolidation therapy following 2 initial weeks of amphotericin B (with or without flucytosine) were also evaluated in 306 patients [11]. In this study, the proportion of patients who displayed a lack of clinical response was similar with fluconazole (32%) and itraconazole (30%). Fluconazole was administered as two loading doses of 800 mg/daily, followed by maintenance with 400 mg, and itraconazole under a loading dose of 600 mg/daily for 3 days, followed by 200 mg twice daily. Toxic effects

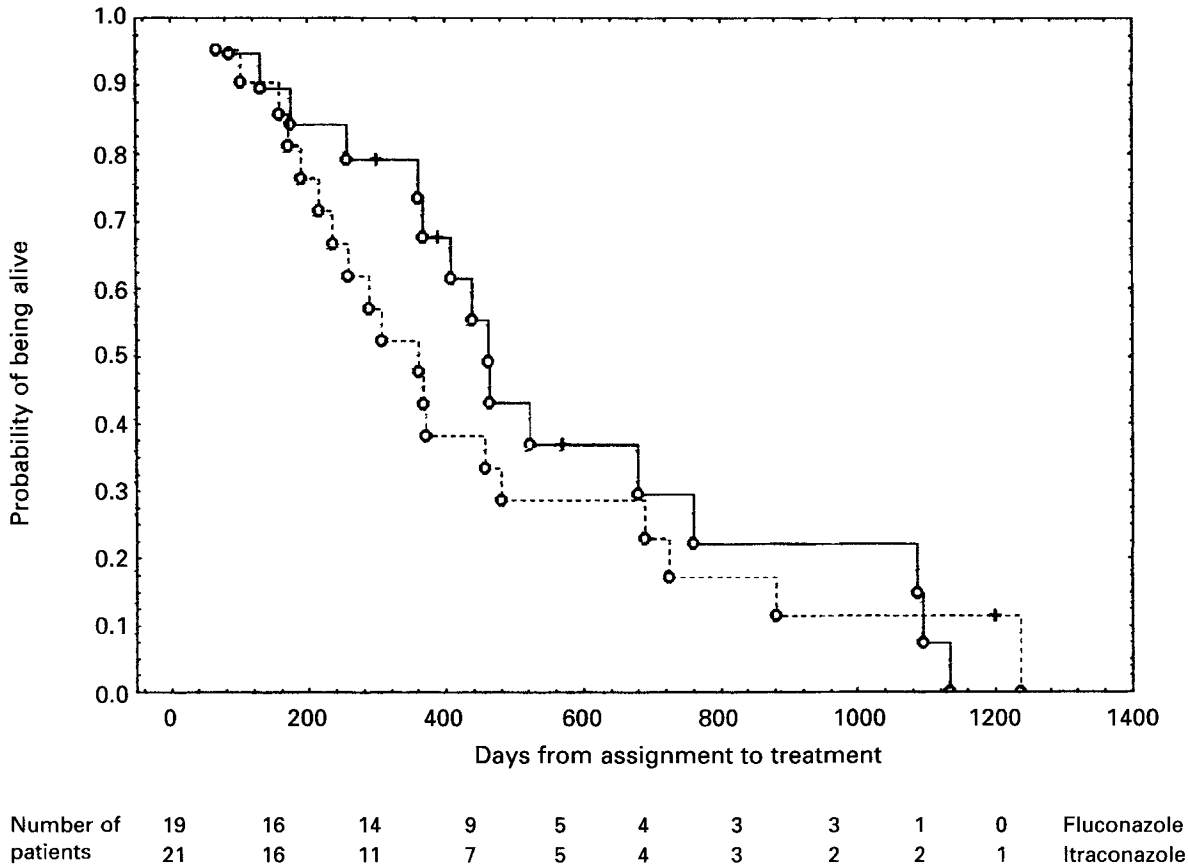

Figure 1 Kaplan–Meier estimates of survival according to treatment group. Five patients were excluded: four were still alive at the end of the study, and one was lost to follow-up, while in good condition, at the 300th day. ....., itraconazole; ——, fluconazole; ○, observed cases; +, excluded cases.

requiring drug discontinuation occurred in 3.14% of patients and were equally distributed between fluconazole and itraconazole.

Despite the limited number of cases, our figures appear to be globally comparable with those reported by the above-cited studies. However, some differences are worth mentioning. The median follow-up length (394.6 days) reported in our study is, to the best of our knowledge, the longest so far reported, and a remarkably lower global relapse rate has been recorded (2.44% versus 14% [7] and 31% [11], respectively).

Although they are of equivalent efficacy, fluconazole appeared to be better tolerated than itraconazole. The side effects requiring drug discontinuation (19% of itraconazole patients) might be related both to the high dosage given in our study and the long follow-up; drug withdrawal was, in fact, recorded at weeks 13, 27 and 87 in three cases, the fourth case having been recorded at week 5.

As serum levels of itraconazole were not determined in our patients, we are unable to explain the occurrence of itraconazole-refractory candidiasis; this is possibly related to the particular pharmacokinetic features displayed by this drug in AIDS patients [12,13]. Monitoring of azole serum levels in the course of lifelong treatment seems, therefore, to be advisable, considering that the occurrence of therapeutic failure associated with an increased MIC of fluconazole has already been documented in the course of long-term therapy in AIDS patients [14].

In conclusion, both fluconazole and itraconazole, given as oral 300-mg capsules once daily, appeared to be equally and highly effective in lifelong suppressive therapy for cryptococcosis in AIDS patients; however, itraconazole may be less well tolerated, especially in long-term administration.

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Ochrobactrum anthropi bacteremia: case report and review of the literature

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Ochrobactrum anthropi is a Gram-negative, motile, non-fermentative, oxidase- and urease-positive, aerobic bacillus, formerly classified as *Achromobacter* species or CDC group Vd, that belongs to the new genus *Ochrobactrum* [1]. The organism is widely distributed in soil, environmental and water sources, including antiseptic solutions and dialysis fluid, and it has been recognized as part of the normal human flora of the large intestine. *O. anthropi* has been rarely described as a human pathogen. Data concerning *O. anthropi* infections are scarce and come mainly from case reports. The majority of the infections were community acquired, and several reports have emphasized how the clinical syndrome caused by *O. anthropi* infection was closely linked to the underlying condition of the host. We report what we believe is the first case of *O. anthropi* non-catheter-related bacteremia in a previously healthy man.

A 47-year-old man was admitted to our hospital complaining of a 10-day history of fever and dry cough. On admission, his temperature was 39°C, the blood pressure was 150/95 mmHg and the pulse was 90/min. Blood was drawn for cultures, and thereafter the patient was given intravenous imipenem (2 g/day). He was a truck driver, and had no prior hospitalization and no underlying disease. He was well until 10 days prior to admission, when he experienced fever to a maximum of 39.5°C, chills, astenia, cough and dysuria. On physical examination, he showed hepatomegaly and diminished breath sounds in both lungs. A chest X-ray showed probable bilateral interstitial infiltrates. Arterial blood gases revealed: pH 7.442, PCO_2 36.5 mmHg and